

### **REMARKS**

Claims 1-22 and 32 were pending in this application. Claims 4, 19, 23-31 and 33 are now cancelled without prejudice to Applicants' right to prosecute their subject matter in the present application and in related applications. New claims 34 and 35 are added. Claims 1, 7-9, 18, 20-22 and 32 are currently amended without any intent of disclaiming equivalents thereof. Accordingly, claims 1-3, 5-18, 20-22, 32, 34 and 35 are pending and presented for consideration.

#### **Claim amendments**

Support for the claim amendments can be found in the specification, including the claims as originally filed. Support for the amendment to claims 1 and 18 is found in original claim 4 and in the specification at least, for example, in paragraphs 31, 44, 45, 52, 53 and 70, and in Figure 1. Support for the amendment to claims 9 and 18 is found in the specification at least, for example, in paragraph 33. Further support for the amendment to claims 18 and 20-22 is found in the specification at least, for example, in paragraph 14. Claims 1, 7-9, 18 and 32 have also been amended for clarification.

Support for new claim 34 is found in the specification at least, for example, in paragraph 53. Support for new claim 35 is found in the specification at least, for example, in paragraph 54.

Applicants submit the amendments to the claims introduce no new matter.

#### **Information Disclosure Statement**

The undersigned wishes to thank the Examiner for forwarding to the Applicants copies of the initialed, signed and dated PTO-1449 forms originally submitted to the Office on December 18, 2001, and on September 12, 2002. However, Applicants respectfully request that the Examiner also consider the art cited in the PTO-1449 form originally submitted to the Office on February 15, 2002, and confirm this by initialing, signing and dating the PTO-1449 form. For convenience, Applicants enclose copies of the February 15, 2002 Information Disclosure Statement, PTO-1449 form, Certificate of First Class Mailing, and a return receipt postcard. Applicants have not resubmitted a copy of the art cited on the February 15, 2002 PTO-1449 form

but would be pleased to do so if requested by the Examiner. Applicants respectfully request that the Examiner return a copy of the initialed, signed and dated PTO-1449 form to the undersigned for completion of Applicants' files.

In addition, Applicants submit together with this response a third supplemental Information Disclosure Statement and accompanying Form PTO-1449 listing publications in accordance with the provisions of 37 C.F.R. §§ 1.97 and 1.98 for consideration by the Examiner in connection with the examination of the present patent application.

*Revocation of Prior Powers/New Power of Attorney and Supplemental Application Data Sheet*

Applicants submit together with this response a Revocation of Prior Powers/New Power of Attorney and a Supplemental Application Data Sheet to update the correspondence information for the present application.

The following comments address in order the remaining issues raised in the Office action.

*Rejections Under 35 U.S.C. § 103(a) over Kenji et al. in view of Noguchi et al.*

Claims 1-4, 7, and 10-13 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Kenji *et al.* (EP 0 476 545) in view of Noguchi *et al.* (US Patent No. 4,843,021). Without acquiescing to the rejection, and solely to advance prosecution, Applicants have cancelled claim 4; the rejection with respect to claim 4 is therefore moot. Applicants traverse the rejection to the extent it is maintained over claims 1-3, 7, and 10-13 as amended.

The proper standard for evaluating obviousness requires a determination of (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Applicant's disclosure. *See id.* citing *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Finally, section 103 requires that the suggestion

or incentive to combine prior art references must be derived from the teachings of the references. *See ACS Hosp. Systems, Inc. v. Montefiore Hosp.* 732 F.2d 1572, 1577, 21 U.S.P.Q. 929, 933 (Fed. Cir. 1984).

The teachings of the primary reference, Kenji *et al.* upon which the Office action relies, is deficient in at least one of the claimed elements. Claim 1, as amended, recites a method to detect an unbound form of a first member of a binding pair by, *inter alia*, “forming a second complex comprising the third member bound to the first member in the first complex and the first particle agglutinated to the second particle” and “detecting the agglutinated first and second particles of the second complex by measuring an increase of the turbidity of the sample thereby detecting the unbound form of the first member in the sample.” Kenji *et al.* teaches a method to detect a target substance by measuring the degree of quenching of fluorescence when a fluorescent-substance-linked particle and a quencher-linked particle are close to one another (*see, e.g.*, Kenji *et al.*, column 2, lines 34-52). Kenji *et al.* does not teach or suggest a method to detect an unbound form of a first member of a binding pair by detecting agglutinated first and second particles by measuring turbidity. Moreover, the secondary reference, Noguchi *et al.*, does not contain any teachings relating to agglutination, in particular detecting first and second particles that are agglutinated. Instead, Noguchi *et al.* describes, as the Examiner suggested, a turbidometric method to detect an antigen/antibody complex in which a particle is joined to the antibody and, in the presence of antigen, forms an antigen/antibody complex (*see, e.g.*, column 5, lines 37-43). Noguchi, like Kenji, is silent with respect to the use of turbidity to detect agglutination of two particles. Therefore, Applicants submit that neither Kenji nor Noguchi teach the required element of detecting the agglutinated first and second particles by measuring an increase in turbidity. Accordingly, Noguchi *et al.* can not properly support a rejection under § 103 because it fails to provide the skilled artisan with the requisite expectation that he or she could successfully practice the claimed subject matter based on the teachings of the reference. Applicants respectfully submit that in view of the above, the combination of Kenji and Noguchi is improper under § 103.

Furthermore, even if, *arguendo*, the disclosures of Kenji *et al.* and Noguchi *et al.* could be properly combined, a skilled artisan would have no expectation of success that the turbidometric method of Noguchi *et al.* combined with the assay of Kenji *et al.* would produce Applicants' invention as claimed in claim 1. As discussed above, amended claim 1 requires detecting the agglutinated first and second particles by measuring an increase of the turbidity of the sample. However, it was known in the art at the time of filing that certain agglutinated particles cause a decrease of the turbidity of a sample (Lim *et al.* (1989) J. Immunol. Methods, 117(2):267-73, a copy of which is attached as Exhibit A). Therefore, Applicants submit that a skilled artisan would have no reason to expect that the method of Noguchi *et al.* combined with the method of Kenji *et al.* would successfully produce Applicants' invention.

Accordingly, Applicants submit that claim 1 and any claims dependent therefrom are novel and unobvious over Kenji *et al.* in view of Noguchi *et al.* Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 1 and dependent claims 2-3, 7, and 10-13.

Rejections Under 35 U.S.C. § 103(a) over Kenji *et al.* in view of Noguchi *et al.* and in further view of Koike *et al.*

Claims 5-6, 8-9, 18-22 and 32 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Kenji *et al.* in view of Noguchi *et al.* and in further view of Koike *et al.* (US Patent No. 5,187,067). Without acquiescing to the rejection, and solely to advance prosecution, Applicants have cancelled claim 19; the rejection with respect to claim 19 is therefore moot. Applicants traverse the rejection to the extent it is maintained over claims 5-6, 8-9, 18, 20-22 and 32 as amended.

As argued above, claim 1 and any claims dependent therefrom are novel and unobvious over Kenji *et al.* in view of Noguchi *et al.* Koike *et al.* does not correct the deficiency of Kenji *et al.* or Noguchi *et al.* Koike *et al.* merely discloses ELISA methods for detecting protein S in a sample using specific antibodies against protein S. Koike *et al.* does not disclose or suggest turbidometric methods for detecting the agglutination of two particles. Koike *et al.* also does not

provide an expectation of success that agglutinated particles would cause an increased turbidity of a sample. Therefore, Applicants submit claim 1 and claims 5-6 and 8-9 dependent therefrom are also novel and unobvious over Kenji *et al.*, Noguchi *et al.* and Koike *et al.*, either alone or in combinations.

Independent claim 18, as amended, relates to a composition or a kit for detecting an unbound form of a first member of a binding pair in a sample comprising a first particle bound to a second member comprising protein S and a second particle bound to a third member comprising C4BP or a fragment thereof and requires that the first and the second particles, when agglutinated, are capable of causing an *increase* of the turbidity of the sample. Kenji *et al.* does not teach or suggest a kit or a composition having a first particle bound to a second member comprising protein S and a second particle bound to a third member comprising C4BP or a fragment thereof. Kenji *et al.* also fails to teach or suggest a first particle and a second particle that, when agglutinated, are capable of causing an increase of the turbidity of the sample. Instead, Kenji *et al.* teaches a first particle linked to a fluorescent substance and a second particle linked to a quencher. It was known that the agglutination of certain particles causes a decrease in turbidity (Lim *et al.* (1989) J Immunol Methods, 117(2):267-73, a copy of which is attached as Exhibit A). Applicants submit that the present application teaches, for example, in paragraphs 52-54, particles with certain parameters, when agglutinated, are capable of causing an increase of the turbidity of a sample.

Neither Noguchi *et al.* nor Koike *et al.* correct the deficiency of Kenji *et al.*. Noguchi *et al.* teaches certain antibodies or antigens immobilized on a latex particle (*see, e.g.*, Noguchi *et al.*, column 4, lines 66-68, and column 5, lines 19-36). Koike *et al.* teaches specific monoclonal antibodies against free protein S that are fixed to an insoluble carrier (*see, e.g.*, Koike *et al.*, column 2, lines 24-48). Neither Noguchi *et al.* nor Koike *et al.* teach or suggest a kit or a composition having a first particle bound to a second member comprising protein S and a second particle bound to a third member comprising C4BP or a fragment thereof. Furthermore, Noguchi *et al.* and Koike *et al.* are silent with respect to whether or not agglutinated particles are capable

of causing an increase in the turbidity of a sample. Therefore, Applicants submit claim 18 and any claims dependent therefrom are novel and unobvious over Kenji *et al.*, Noguchi *et al.* and Kokie *et al.*, alone or in combination.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5-6, 8-9, 18, 20-22 and 32.

Rejections Under 35 U.S.C. § 103(a) over Kenji *et al.* in view of Noguchi *et al.* and in further view of Mischak *et al.*

Claims 14-17 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Kenji *et al.* in view of Noguchi *et al.* and in further view of Mischak *et al.* (US Patent No. 6,124,430). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

As discussed above, claim 1 and any claims dependent therefrom including claims 14-17 are novel and unobvious over Kenji *et al.* and Noguchi *et al.*, alone or in combination. Mischak *et al.* does not correct the deficiency of Kenji *et al.* or Noguchi *et al.*. Mischak *et al.* teaches a method for rapid and direct quantification of hBNP levels in biological fluids using specific antibodies against hBNP. Mischak *et al.* is silent with respect to turbidometric methods or agglutination assays. Mischak *et al.* also does not provide an expectation of success that agglutinated particles would cause an increase of the turbidity of a sample. Therefore, Applicants submit claim 1 and any claims dependent therefrom are novel and unobvious over Kenji *et al.*, Noguchi *et al.* and Mischak *et al.*, either alone or in combination. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 14-17.

**CONCLUSION**

Applicants believe that all of the art of record has been overcome and claims 1-3, 5-22, 32, 34 and 35 are in condition for allowance. The Examiner is invited to telephone the undersigned agent to discuss any remaining issues. Early and favorable actions are respectfully solicited.

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Reg. No. 51,551

Tel. No.: (617) 261-3198  
Fax No.: (617) 261-3175  
Customer Number: 022832

Respectfully submitted,

A handwritten signature in dark ink, appearing to read 'Fangli Chen', is written over a horizontal line.

Fangli Chen, Ph.D.  
Agent for Applicants  
Kirkpatrick & Lockhart Nicholson Graham LLP  
75 State Street  
Boston, Massachusetts 02109